REMARKS

I. Status of the Claims

Claims 7, 9, 11–13, 30–32, 34, and 35 were pending in the application. Upon entry of this amendment, claims 30, 32 and 38–42 are pending. Claims 30 and 32 have been amended. Claims 7, 9, 11–13, 31, and 34–37 are cancelled. Claims 1–6, 8, 10, 14–29, and 33 were previously cancelled. Claims 38–42 are newly added.

Throughout this response, references made to paragraphs of the specification are made to the paragraph numbering in the publication US2005/0227917.

Claim 30 has been amended be directed to a method of assessing the risk of having colon cancer in a human patient by determining a level of a nucleic acid and a level of at least one molecular marker gene, and to state that the nucleic acid comprises "the nucleotide sequence of SEQ ID NO: 23702." Support for these amendments may be found throughout the specification and in particular, at paragraphs [0113], [0172], [0184], [0633], and [1169].

Claim 30 has also been amended to recite "comparing said level of the nucleic acid in (a) to a control level of the nucleic acid," and "comparing said level of the at least one molecular marker gene in (a) to a control level of the at least one molecular marker gene." Support for these amendments may be found throughout the specification and in particular, at paragraphs [0144], [0172], [0184], and [0633].

Claim 30 has been further amended to recite "wherein at least a two-fold increase between the level of the nucleic acid in (a) and the control level of the nucleic acid, and a change in levels of expression between the level of the at least one molecular marker gene in (a) and the control level of the at least one molecular marker gene indicate that the patient has an increased risk of having colon cancer." Support for this amendment may be found throughout the specification and in particular, at paragraphs [0033], [0113], [0144], [0172], [0184], [0633], [1168], and [1169].

Claim 32 has been amended to recite "wherein the at least a two-fold increase is at least a five-fold increase compared with the control level of the nucleic acid." Support for this amendment may be found throughout the specification and in particular, at paragraphs [0033], and [0144].

Newly added claims 38–40 correspond to the subject matter of cancelled claims 11–13. Support for these claims may be found throughout the specification and in originally filed claims 11, 12, and 13.

Newly added claims 41 and 42 are directed to methods of assessing the risk of having breast and prostate cancer, respectively, and are similar to amended claim 30. Support for these claims may be found throughout the specification and in particular, at paragraphs [0033], [0113], [0144], [0172], [0184], [0633], [1168], and [1169].

No new matter has been added and therefore entry of the amendments is respectfully requested.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants request reconsideration of the pending claims in view of the following remarks.

II. Priority

Applicants acknowledge that the effective filing date of the instant application is December 23, 2003 which is the filing date of Provisional Application 60/532,830.

III. Claim Objections

Claim 9 is objected to under 37 CFR 1.75(c), as allegedly being improper dependent form for failing to further limit the subject matter of a previous claim. In particular, the Office alleges that claim 9 "is drawn to the method of claim 7, wherein the gene product is a nucleic acid.

However, claim 7 already requires the gene product to be a nucleic acid," (page 4 of the Office Action).

As claim 9 has been cancelled, this objection is now moot. Applicants thus respectfully request that this basis for objection be withdrawn.

IV. Claim Rejections Under 35 USC § 112, Second Paragraph

Claim 36 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for lacking sufficient antecedent basis for the limitation "the patient sample."

As claim 36 has been cancelled, this rejection is now moot. Applicants thus respectfully request that this basis for rejection be withdrawn.

V. Claim Rejections Under 35 USC § 112, First Paragraph, Enablement

Claims 7, 9, 11–13, 30-32 and 34–37 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office maintains that the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

As a preliminary matter, Applicants respectfully point out that claim 7 and all dependent claims therefrom have been cancelled, making their rejection moot.

To the extent that the rejection applies to the amended claims, Applicants respectfully maintain traversal of the rejections and its supporting remarks. However, in the interest of expediting prosecution, Applicants have amended the claims to be directed to methods of assessing the risk of a human patient having colon cancer by: (a) determining the level of a nucleic acid comprising the nucleic acid sequence SEQ ID NO: 23702 and the level of at least one molecular marker gene in a patient sample; (b) comparing the level of the nucleic acid comprising SEQ ID NO: 23702 in the patient sample to a control level of the nucleic acid; and (c) comparing the level of

the at least one molecular marker gene in the patient sample to a control level of the at least one molecular marker gene; where at least a two-fold increase between the level of the nucleic acid comprising SEQ ID NO: 23702 in the patient sample and the control level of the nucleic acid, and a change in levels of expression between the level of the at least one molecular marker gene in the patient sample and the control level of the at least one molecular marker indicate that the patient has an increased risk of having colon cancer. In other embodiments claims are directed to assessing the risk of a human patient having breast cancer, and in still other embodiments claims are directed to assessing the risk of a human patient having prostate cancer.

Applicants respectfully assert that the currently amended claims have more than adequate support in the specification to enable one of skill in the art to make and use the claimed invention commensurate in scope with the claimed invention. For example, the specification teaches that SEQ ID NO: 23702 expression data and expression data from at least one molecular marker gene can be easily obtained from a patient sample suspected of being cancerous by various known methods, such as contacting the sample with probes specific for the nucleic acid comprising the nucleotide sequence of SEQ ID NO: 23702 and for the at least one molecular marker gene (see paragraph [0127]); and that the expression data of SEQ ID NO: 23702 can be used in combination with the expression data of the at least one molecular marker gene to assess the risk of having cancer (see paragraph [0632]) by comparing the expression data from a patient sample to a control level of expression of SEQ ID NO: 23702 and a control level of expression of the at least one molecular marker gene (see paragraph [0144]). Further, several working examples in the specification disclose the use of differentially expressed genes as a risk assessment tool to be used in combination with other methods for evaluating a patient's cancer phenotype. Paragraph [0632] embodies this practice by stating "The differential expression of these polynucleotides can be used as a diagnostic marker, a prognostic marker, for risk assessment, patient treatment and the like. These polynucleotide sequences can also be used in combination with other molecular and/or biochemical markers." Moreover, Example 105 of the specification is a working example showing that metastatic colon cancer cells have a statistically significant two-fold over-expression of SEQ ID NO: 23702 (see paragraph [1168]) as compared to a control level of SEQ ID NO: 230702 expression in an unmatched control, which is a pooled sample of normal colon cells from numerous

healthy patients (see paragraph [1169] under experiment 4). Example 105 further shows that breast and prostate cancerous cells from patient tumor samples also have a statistically significant at least two-fold over-expression of SEQ ID NO: 23702 as compared to control levels of expression of SEQ ID NO: 23702 in matched controls containing non-cancerous cells taken from the same patients where the tumor samples were obtained. Applicants note that while the breast and prostate cancer data in Example 105 utilized matched control samples derived from the same patient having a known cancer status, it would be clear to one of skill in the art that when using the claimed methods of assessing the risk of having cancer on a patient with an unknown cancer status, the expression data of SEQ ID NO: 23702 and the at least one molecular marker would be compared to control levels of each gene derived from normal, cancer-free samples that are not obtained from the same patient. This is clear from the amended claims, which require comparison to a control level of expression; and from the specification, which teaches that a control level of expression is obtained from an individual not having cancer (see paragraph [0144]).

Thus, the teachings in the specification and the data presented in Example 105 clearly teach one of skill that the expression level of SEQ ID NO: 23702 can be used in combination with the expression level of at least one molecular marker gene to assess whether a patient has an increased risk of having colon, breast, or prostate cancer.

The Office asserts that undue experimentation would be required to perform the claimed methods. In order to be fully responsive, below are Applicants' responses to the Office's specific remarks in the Response to Arguments section of the Office Action.

Undue Experimentation

The Office maintains that while one of ordinary skill in the art could perform the experimentation required utilizing known methods in molecular biology, the experimentation would be undue, as "the amount of experimentation and the analysis of the results obtained during the experimentation would be unpredictable and non-routine" (middle of page 23 of the Office Action). The Office also alleges that the undue experimentation is required, as the specification provides only minimal guidance and that this lack of guidance combined with the inherent unpredictability in the claimed methods would require undue experimentation.

However, with respect to undue experimentation, MPEP § 2164.01 states that, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)."

Applicants respectfully point out that, as amended, the claims are not directed to detection or identification of cancer based solely on the expression level of SEQ ID NO: 23702. Rather, the claims are directed to using the expression level of SEQ ID NO: 23702 and the expression level of at least one molecular marker gene to help assess a patient's risk of having colon, breast, or prostate cancer wherein at least a two-fold increase in the expression level of SEQ ID NO: 23702 and a change in the level of expression of the at least one molecular marker gene indicate an increased risk of having colon, breast, or prostate cancer. Applicants note that risk assessment is distinct from detection or identification of cancer, as risk assessment provides information regarding the likelihood of having cancer and does not provide definitive information regarding the presence or absence of cancer. Accordingly, over-expression of SEQ ID NO: 23702 in a sample may be indicative, but not definitive, of a cancerous phenotype. The additional requirement of determining expression of at least one molecular marker gene clarifies that evaluating over-expression of SEQ ID NO: 23702 in a patient sample is only one parameter used in evaluating risk of having cancer. Thus, over-expression of SEQ ID NO: 23702 is used in combination with other risk assessment tools, such as detecting differential expression of at least one molecular marker gene, in evaluating the risk of a patient having cancer.

As discussed above, the claimed methods of assessing the risk of having cancer by determining the expression level of SEQ ID NO: 23702 and the expression level of at least one molecular marker gene are supported by the specification. The data in Example 105 demonstrate a statistically significant two-fold increase in SEQ ID NO: 23702 expression in a tumor sample taken

from a specific population of colon, breast, and prostate cancer patients. The specification also teaches that expression data of at least one molecular gene marker, such as one of the many cancer genes known in the art, can be used in combination with the SEQ ID NO: 23702 over-expression data. As such, one of skill in the art would be able to use this expression data, in combination with other diagnostic tests commonly performed in the art, to assess a patient's risk of having cancer.

Thus, making and using the invention requires only routine molecular biology techniques and is a matter of routine testing of colon, breast, or prostate samples for expression of SEQ ID NO: 23702 and expression of at least one molecular marker gene.

Correlation Between SEQ ID NO: 23702 Expression and Cancer

The Office alleges that one of skill in the art would have to demonstrate that over-expression of SEQ ID NO: 23702 only occurs in cancerous breast, colon, or prostate tissue from cancer patients and not in breast, colon, or prostate tissue from cancer-free individuals, as working Example 105 does not include a comparison to a cancer-free, normal control. The Office further alleges that "it cannot be concluded from the data presented in Example 105 that the required correlation between the expression level of SEQ ID NO: 23702 and breast cancer, colon cancer, and prostate cancer exists" (bottom of page 25 to top of page 26 of the Office Action).

Applicants respectfully point out that Example 105 does include a comparison of metastasized cancerous colon cells to a cancer-free, normal control. As discussed above, expression of SEQ ID NO: 23702 in metastasized cancerous colon cells was compared to that of a pooled sample of normal colon from many individuals (see paragraph [1169]). Given that the pooled sample corresponds to healthy, cancer-free individuals, the data in Table 159 clearly demonstrates that SEQ ID NO: 23702 is only over-expressed in cancerous colon cells, and not in normal colon cells from healthy individuals. Thus, Applicants respectfully assert that the expression level of SEQ ID NO: 23702 is correlated with colon cancer, as Example 105 demonstrates that SEQ ID NO: 23702 over-expression only occurs in cancerous colon cells.

Applicants also note that the other tested samples described in Example 105 were compared to matched controls from the same patient, meaning that the normal cell samples were obtained from the same tissue as the cancerous (i.e., tumor) cell samples. For example, a breast tumor cell sample from a patient was compared to a normal breast cell sample from the same patient. It is well understood in the art that normal, cancer-free cells can be collected from the same tissue containing a tumor and used as a matched negative control to compare the expression level of a given gene in the tumor. Normal, cancer-free cells from a tissue containing a tumor can be used, as the tumor is genetically and morphologically distinct from the surrounding normal tissue. It is therefore routine in the art to identify and collect normal, cancer-free cells from a tissue containing a tumor. Furthermore, using matched controls has many advantages, such as eliminating many of the variables inherent in comparing samples from different individuals. For example, matched controls eliminate variability that may be associated with single nucleotide polymorphisms (SNPs). Given that matched controls are equivalent to unmatched controls from healthy, cancer-free patients, the data in Example 105 demonstrate that SEQ ID NO: 23702 is over-expressed in cancerous breast, and prostate cells; but not in normal, non-cancerous breast, and prostate cells. Thus, one of skill in the art would understand that the data in Example 105 show a correlation between the expression level of SEQ ID NO: 23702 and breast and prostate cancer.

Variability of Data in Example 105

The Office alleges that "The high levels of variability in the results obtained from patients known to have breast cancer, colon cancer, or prostate cancer suggests that the claimed methods are associated with a high degree of variability and unpredictability" (middle of page 24 of the Office Action).

Applicants respectfully maintain that this variability in the data is irrelevant, as only routine experimentation is required to reliably perform the claimed methods of assessing the risk of having cancer. As discussed above, assessing the risk of having cancer is distinct from detecting or identifying cancer, and does not require that every patient tested show an increase in expression of SEQ ID NO: 23702. Over-expression of SEQ ID NO: 23702 is merely one indictor used in

evaluating the likelihood that a given patient has cancer, which is reflected in the claimed methods of assessing the risk of having cancer by including the additional requirement that the expression level of at least one molecular marker gene be determined. It is the combined expression data from SEQ ID NO: 23702 and the at least one molecular marker gene that is used to evaluate the risk of having colon, breast, or prostate cancer. As the claims are directed to assessing the risk of having cancer and not to detecting or identifying cancer, it is sufficient to know that SEQ ID NO: 23702 is significantly over-expressed in cancerous colon, breast, and prostate cells, when compared with normal, cancer-free cells, in a certain percentage of patients.

The Office further alleges that "the variability in the results presented in Example 105 suggests that even methods of risk assessment could only be reliably performed after conducting an extensive amount of additional non-routine experimentation, in particular, to account for the fact that the results obtained in Example 105 do not include results obtained from normal, cancer-free individuals" (middle of page 26 of the Office Action).

Applicants respectfully point out that Example 105 in the specification does include a comparison of metastasized cancerous colon cells to a cancer-free, normal control (see discussion above), thus establishing a correlation between the expression level of SEQ ID NO: 23702 and colon cancer. However, it is not necessary to obtain results from normal, cancer-free individuals, as it is well known in the art that using matched controls (i.e., normal, cancer-free cells from the same tissue as the tumor cells) is equivalent to using controls from normal, cancer-free individuals and has the advantage of reducing variability inherent to comparing samples for different individuals. Thus, one of skill in the art could reliably perform the claimed methods of assessing the risk of having colon cancer, breast cancer, or prostate cancer without conducting non-routine experimentation.

Using SEQ ID NO: 23702 Expression to Assess Risk of Having Cancer in Ethnic Populations

With respect to the Office's allegation regarding determining the ethnic populations in which the expression of SEQ ID NO: 23702 can be used to reliably assess the risk of having cancer, Applicants are not aware of any generally accepted teaching in the art suggesting that different ethnic populations develop cancer through distinct mechanisms. On the contrary, it is well known in the art that cancers such as colon, breast, and prostate cancer, are broad diseases that arise through many different mechanisms, any of which could affect an individual from the general population. Thus, a gene, such as SEQ ID NO: 23702, that has been shown to be differentially expressed in cancer can be used to assess the risk of a patient from the general population having cancer. Furthermore, Applicants note that the expression data of SEQ ID NO: 23702 will be used in combination with expression data from at least one of the many molecular marker genes known in the art. It is well known in the art that molecular marker genes, such as cancer genes, can be used to assess the risk of a patient from the general population having cancer. Accordingly, one of skill in the art would not have to perform any undue experimentation to use the expression data of SEQ ID NO: 23702 in combination with at least one molecular marker to reliably assess the risk of having colon, breast, or prostate cancer for patients of all ethnicities.

Use of Variants of SEQ ID NO: 23702 to Assess Risk of Having Cancer

Applicants further note that as amended, the pending claims no longer encompass a large number of variants, as the claims are directed to determining the expression of a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 23702. Thus, the Office's concerns regarding "which variants of SEQ ID NO: 23702 are capable of functioning as reliable identifiers of cancerous cells or indicators of cancer" (see bottom of page 23 of the Office Action), are moot.

Conclusion

In view of the above, Applicants respectfully submit that a person skilled in the art would be able to assess the increased risk of colon, breast, or prostate cancer based on the over-expression of SEQ ID NO: 23702 and the change in level of expression of at least one molecular marker gene using the teachings of the present application without undue experimentation. Applicants thus respectfully request that this basis for rejection be withdrawn.

VI. Claim Rejections Under 35 USC § 112, First Paragraph, Written Description

Claims 7, 9, 11-13, 30–32 and 34–37 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Offices maintains that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

As a preliminary matter, Applicants respectfully note that claim 7 and all dependent claims therefrom have been cancelled, making their rejection moot.

To the extent that the rejection applies to the amended claims, Applicants respectfully maintain their traversal of the rejection and its supporting remarks.

The Office alleges that the specification does not contain an actual reduction to practice of risk assessment, "since the only working example utilizes samples obtained from patients whose cancer status is known" (see top of page 27 of the Office Action). The Office further alleges that "the specification fails to teach the relevant identifying characteristics necessary to practice the invention, because the data presented in the only relevant working example does not establish that a correlation exists between the expression level of the claimed nucleic acid and breast cancer, colon cancer, and prostate cancer" (see page 27 of the Office Action).

Applicants respectfully assert that the Office is using the wrong standard in support of the written description rejection by requiring that there be an actual reduction to practice of the claimed invention. MPEP 2163 § (a)(1) makes clear that "the written description standard may be met ... even where actual reduction to practice of an invention is absent." Moreover, all that is required is that an ordinary artisan would reasonably conclude that Applicant was in possession of the claimed invention at the time of filing (see MPEP § 2163). Additionally, MPEP § 2163 (I) makes clear that possession of the claimed invention may be shown by describing the claimed invention "using such descriptive means as words. structures, figures, diagrams, and formulas that fully set forth the claimed invention."

Applicants respectfully point out that the specification fully describes and sets forth the claimed invention, which, as amended, is directed to using the expression level of SEQ ID NO: 23702 and the expression level of at least one molecular marker gene to help assess a patient's risk of having colon, breast, or prostate cancer wherein at least a two-fold increase in the expression level of SEQ ID NO: 23702 as compared to a control level of expression, and a change in the level of expression of the at least one molecular marker gene, as compared to a control level of expression, indicate an increased risk of having colon, breast, or prostate cancer. For example, the specification teaches that SEQ ID NO: 23702 expression data can be used in combination with expression data of at least one molecular marker gene to assess the risk of having colon cancer, breast cancer, and prostate cancer (see paragraph [0632]). The specification also teaches that at least a two-fold increase in expression of SEQ ID NO: 23702 and a change in the expression level of at least one molecular marker are useful in assessing risk of having colon cancer, breast cancer, and prostate cancer (see paragraphs [0033], [0172], and [1168]. Further, the specification teaches that the SEQ ID NO: 23702 expression data from a patient sample is compared to a control level of SEQ ID NO: 23702 expression, and that the expression data of at least one molecular marker gene is compared to a control level of expression of the at least one molecular marker gene (see paragraphs [0113], [0144], and [1169]).

Further, and while not required, Applicants respectfully note that, as described in detail in the enablement section above, the data of Example 105 above show that the statistically significant, two-fold over-expression of SEQ ID NO: 23702 is correlated to cancer in a certain population of colon, breast, and prostate cancer patients. For colon cancer, the correlation is based on the comparison of SEQ ID NO: 23702 expression in cancerous colon cells to SEQ ID NO: 23702 expression in a pooled sample of normal, cancer-free cells from normal individuals. For breast and prostate cancer, the correlation is based on the comparison of SEQ ID NO: 23702 expression in cancerous breast and prostate cells to SEQ ID NO: 23702 expression in matched controls that are equivalent to normal, cancer-free cell samples from normal individuals. Thus, Applicants respectfully submit that the data in Example 105 establishes a correlation between the expression level of SEQ ID NO: 23702 and colon, breast, and prostate cancer.

In view of the above, Applicants respectfully submit that one of ordinary skill in the art would recognize that Applicants had possession of the claimed invention at the time of filing of the application. Applicants thus respectfully request that this basis for rejection be withdrawn.

VII. Prior Art

Applicants thank the Examiner for acknowledging that the claimed methods are free of art.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **Docket No. 223002106600**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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